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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/756,948	01/13/2004	Martin W. Brechbiel	4239-67017-01	3278

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EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	**PAPER NUMBER**
1618	

MAIL DATE	DELIVERY MODE
09/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/756,948	BRECHBIEL ET AL.	
	Examiner	Art Unit	
	Melissa Perreira	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-33 are pending in the application. Any objections and/or rejections from previous office actions that have not been reiterated in this office action are obviated.

1. The declaration under 37 CFR 1.132 filed 7/31/07 is sufficient to overcome the rejection of claims 1-33 based upon the admission that the Kobayashi (I-III) references are not by others and are not prior art.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suga et al. (*Acta Radiologica* **2003**, *44*, 35-42) in view of Li et al. (US 7,261,875B2) and further in view of Baker, Jr. et al. (US 6,471,968B1).

3. Suga et al. (*Acta Radiologica* **2003**, *44*, 35-42) discloses the method of identifying a lymph node into which lymph fluid flows from a tumor for breast sentinel lymph node (first lymph node) mapping (p35, paragraph 1; p36, paragraph 2). The method involves imaging the lymph node and lymphatic vessel draining from the injection site using MR lymphography and the contrast agents used are gadopentetate

dimeglumine, Gd-DTPA-PE-POE and SPIO particles (p36, paragraph 2; p37, results; p41, paragraph 7). MR lymphography is advantageous for visualizing focal lymph draining from a breast tumor since the results show that MR lymphography provided for visualization only of the lymphatic drainage from the injection site of the contrast agents. Upon peritumoral or periareolar injection of the contrast agent, visualization of lymphatic drainage from early state breast tumors was accomplished (p41, paragraphs 4 and 5). Also disclosed is that surgical biopsy of the sentinel lymph node is a standard practice for minimally invasive surgery in early stages of breast cancer (p35, paragraph 1). Suga et al. does not disclose the use of PAMAM contrast agents for the method of identifying a lymph node into which lymph fluid flows from a tumor.

4. Li et al. (US 7,261,875B2) discloses Gd-DTPA-PAMAM (DAB-AM-4, DAB-AM-8, etc. column 9, lines 21-27) dendritic diagnostic (MRI) contrast agents (column 3, line 15; column 4, lines 8-23; column 16, line 26) that may include fluorescent probes, diagnostic agents for cancer, therapeutic agents, etc. (column 4, lines 65+). These contrast agents may be of generation 0-7 (table 1). The polymer carrier (PAMAM) is useful to provide for improved retention of the conjugates (contrast agents) in target regions, increased solubility of water-insoluble agents and allow for reduced dose which decreases in systemic toxicity (column 1, lines 40-45; column 2, lines 56-60; column 11, lines 32-34). The contrast agents/therapeutic agents of the disclosure may be used to treat cancer of the lymph node (column 18, lines 15-19) and different doses are provided (column 19, lines 4-31).

5. Brechbiel et al. (US 7,081,452B2) discloses a stable 1B4M-DTPA chelate as a potential chelate for the delivery of radiometals to tumor cells as an alternative to DTPA or DOTA chelates. DTPA and DOTA chelates have a potential for radiotoxicity of non-tumor cells (normal tissue) and therefore more stable chelates are desirable (column 2, lines 13-40).

6. Baker, Jr. et al. (US 6,471,968B1) discloses the use of a fluorescent tagged (column 7, lines 7) Gd-PAMAM dendrimer conjugate (column 3, line 13; column 6, line 63) for visualizing the location of diseased cells, such as a tumor and monitoring the response to therapy via MR imaging (column 2, lines 30-40; column 10, lines 65+ to column 11, lines 1-5). The fluorogenic marker not only allows for the locating of a tumor but also allows for the visualization of response to treatment with therapeutic agents.

7. At the time of the invention it would be obvious to one ordinarily skilled in the art to utilize (try) a Gd-DTPA-PAMAM contrast agent (Li et al.) for the method of identifying a lymph node into which lymph fluid flows from a tumor (Suga et al.). The substitution of the PE-PEO of Gd-DTPA-PE-POE for the PAMAM polymer and 1B4M-DTPA chelate for DTPA would be obvious to try as PAMAM polymer provides for increased solubility of water-insoluble agents, allows for decreased dose administration and 1B4M-DTPA chelate provides stability as well as that stated above. The increased generation, such as G-8 of the PAMAM dendrimer would be advantageous to allow for high loading of the therapeutic diagnostic agents and a spherical morphological structure (Li et al. column 7, lines 44-45; column 8, lines 65-66). Also, it would have been obvious to one skilled in the art to inject the PAMAM dendrimer contrast agent into a tumor site (intratumorally)

to visualize the lymphatic vessel draining from the tumor site as Suga et al. discloses that MR lymphography provides for visualization from the site of injection of the contrast agent or peritumorally as is described above. The importance of surgical biopsy of the sentinel lymph node is described for early stages of breast cancer and it is advantageous to use this procedure concurrently with the technique of imaging the lymphatic system with the PAMAM dendrimer contrast agents as they allow for a more reliable method of detecting tumors in the lymphatic system. This will guarantee that the correct site is being biopsied. It would be obvious and advantageous to use a fluorescent tag attached to the Gd-DTPA-PAMAM contrast agent (Li et al.) in order to monitor the response to the treatment of tumors found in the lymphatic system to assure that the cancer has been fully eradicated due to the response to treatment.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Perreira whose telephone number is 571-272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MP
August 29, 2007

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER